AMENDMENTS TO THE CLAIMS

1. (Currently Amended) An *in vitro* method of determining activation or inactivation of the atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) hormonal systems in a subject, the method comprising simultaneously detecting in a single reading, in a single assay the presence or proportionally cumulative amount of atrial and brain natriuretic peptide prohormones (proANP and proBNP) or fragments thereof in a sample from the subject, wherein detection of the presence or an increase in the proportionally cumulative amount of proANP and proBNP, or fragments thereof, in the sample indicates activation of the ANP and BNP hormonal systems, and detection of a decrease in the proportionally cumulative amount of proANP and proBNP, or fragments thereof, in the sample indicates inactivation of these systems.

2. (Currently Amended) The method according to claim 1, which comprises contacting the sample with a bi- or oligo- specific first binding substance that is able to bind to ~~both~~:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3);

(ii) a homologous sequence having at least 70% identity to (a)(i); or

(iii) a fragment of (a)(i) or (a)(ii) which is at least 6 amino acids in length;

~~and~~

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ ID NO:6);

(ii) a homologous sequence having at least 70% identity to (b)(i); or

(iii) a fragment of (b)(i) or (b)(ii) which is at least 6 amino acids in length; and

(c) a fusion polypeptide agent comprising both (a) and (b).

3. (Currently Amended) The method according to claim 1 which comprises contacting the sample with

- ~~an~~ a fusion polypeptide agent comprising both:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3);

(ii) a homologous sequence having at least 70% identity to (a)(i); or

(iii) a fragment of (a)(i) or (a)(ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ ID NO:6);

(ii) a homologous sequence having at least 70% identity to (b)(i); or

(iii) a fragment of (b)(i) or (b)(ii) which is at least 6 amino acids in length.

and/~~or~~

- a first binding substance which is able to bind to:

(c) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3);

(ii) a homologous sequence having at least 70% identity to (c)(i); or

(iii) a fragment of (c)(i) or (c)(ii) which is at least 6 amino acids in length;

~~and~~

(d) (i) proBNP ~~pro-BNP~~ (SEQ ID NO:4), BNP (SEQ ID NO:5) or NT-proBNP (SEQ ID NO:6);

(ii) a homologous sequence having at least 70% identity to (d)(i); or

(iii) a fragment of (d)(i) or (d)(ii) which is at least 6 amino acids in length; and

(e) said fusion polypeptide agent.

4. (Previously Presented) The method according to claim 3 wherein the first binding substance comprises:

(a) a bi- or oligo-specific binding substance; or

(b) a mixture of mono-specific binding substances.

5. (Currently Amended) The method according to claim 2 wherein the first binding substance comprises:

(a) natriuretic receptor GC-A (SEQ ID NO: 33);

(b) ~~a homologous sequence having at least 70% identity to (a);~~ or

~~(c)~~ a fragment of (a) ~~or (b)~~ which is at least 400 amino acids in length.

6. (Previously Presented) The method according to claim 5 wherein the first binding substance comprises an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO: 34).

7. (Previously Presented) The method according to claim 2 wherein the first binding substance comprises an antibody or a fragment or derivative thereof.

8. (Previously Presented) The method according to claim 7 wherein the antibody comprises a polyclonal antibody, monoclonal antibody, oligoclonal antibody, bifunctional antibody or crossreacting polyclonal antibody.

9. (Currently Amended) The method according to claim 3 wherein in the fusion polypeptide agent, (a)(i) is SEQ ID NO:3 and (b)(i) is SEQ ID NO: 6 or (a)(i) is SEQ ID NO:2 and (b)(i) is SEQ ID NO:5.

10. (Currently Amended) The method according to claim 3 wherein the fusion polypeptide agent comprises ~~or consists of~~:

(a) proBNP$_{15-24}$ and proANP$_{82-96}$;

(b) proBNP$_{1-37}$ and proANP$_{29-98}$;

(c) proBNP$_{10-29}$ and proANP$_{20-80}$;

(d) proBNP$_{1-76}$ and proANP$_{1-98}$;

(e) proBNP$_{10-29}$ and proANP$_{60-80}$;

(f) proBNP$_{1-108}$ and proANP$_{1-126}$; or

(g) proBNP$_{77-92}$ and proANP$_{112-126}$.

11. (Currently Amended) The method according to claim 3 wherein the fusion polypeptide agent is a peptide ~~polypeptide~~.

12. (Previously Presented) The method according to claim 2 wherein the first binding substance and/or the fusion polypeptide agent is:

(a) labelled with a detectable label; and/or

(b) immobilised.

13. (Previously Presented) The method according to claim 2 which additionally comprises contacting the sample with a second binding substance which is able to bind to the first binding substance.

14. (Previously Presented) The method according to claim 13 wherein the second binding substance is:

(a) labelled with a detectable label; and/or

(b) immobilised.

15. (Previously Presented) The method according to claim 13 wherein the second binding substance causes precipitation of the first binding substance and any peptide which is bound to it.

16. (Previously Presented) The method according to claim 1 which comprises an immunoassay.

17. (Previously Presented) The method according to claim 1, wherein said method is diagnostic of heart failure or monitors treatment of a cardiac condition.

18. (Currently Amended) ~~An~~ A fusion polypeptide agent which comprises both:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3);

(ii) a homologous sequence having at least 70% identity to (a)(i); or

(iii) a fragment of (a)(i) or (a)(ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a homologous sequence having at least 70% identity to (b)(i); or

(iii) a fragment of (b)(i) or (b)(ii) which is at least 6 amino acids in length.

19. (Currently Amended) ~~An~~ The fusion polypeptide agent according to claim 18 which comprises ~~or consists of~~:

(a) $proBNP_{15-24}$ and $proANP_{82-96}$;

(b) $proBNP_{1-37}$ and $proANP_{29-98}$;

(c) $proBNP_{10-29}$ and $proANP_{20-80}$;

(d) $proBNP_{1-76}$ and $proANP_{1-98}$;

(e) $proBNP_{10-29}$ and $proANP_{60-80}$;

(f) $proBNP_{1-108}$ and $proANP_{1-126}$; or

(g) $proBNP_{77-92}$ and $proANP_{112-126}$.

20. (Currently Amended) ~~An~~ The fusion polypeptide agent according to claim 19 (a)-(g) which comprises any one of SEQ ID NOs:13, 14, 15, 17, 18, 19 or 20, respectively.

21. (Currently Amended) ~~An~~ The fusion polypeptide agent according to claim 18 which is labelled with a detectable label.

22. (Cancelled).

23. (Currently Amended) A polynucleotide comprising sequence which encodes a fusion polypeptide agent according to claim ~~22~~ 18 or sequence which is complementary to the coding sequence.

24. (Previously Presented) A polynucleotide according to claim 23 which comprises both:

(a) (i) SEQ ID NOs:7, 8 or 9;

(ii) a sequence complementary to (a)(i);

(iii) a sequence which hybridises under medium or high stringent conditions to (a)(i) or (a)(ii);

(iv) a sequence which is degenerate as a result of the genetic code to (a)(i), (a)(ii) or (a)(iii);

(v) a sequence having at least 70% identity to any of the sequences in (a)(i) to (a)(iv); or

(vi) a fragment of any of the sequences in (a)(i) to (a)(v), wherein said fragment encodes a peptide of at least six amino acids in length;

and

(b) (i) SEQ ID NOs:10, 11 or 12;

(ii) a sequence complementary to (b)(i);

(iii) a sequence which hybridises under medium or high stringent conditions to (b)(i) or (b)(ii);

(iv) a sequence which is degenerate as a result of the genetic code to (b)(i), (b)(ii) or (b)(iii);

(v) a sequence having at least 70% identity to any of the sequences in (b)(i) to (b)(iv); or

(vi) a fragment of any of the sequences in (b)(i) to (b)(v), wherein said fragment encodes a peptide of at least six amino acids in length.

25. (Previously Presented) An expression vector comprising a polynucleotide according to claim 23.

26. (Previously Presented) A host cell comprising a polynucleotide according to claim 23.

27. (Currently Amended) A process for producing a fusion polypeptide agent according to claim ~~22~~ 18 which process comprises:

(I) cultivating a host cell comprising a polynucleotide, or its complement, which encodes a polypeptide which comprises both:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2) or NT-proANP (SEQ ID NO:3);

(ii) a homologous sequence having at least 70% identity to (a)(i); or

(iii) a fragment of (a)(i) or (a)(ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a homologous sequence having at least 70% identity to (b)(i); or

(iii) a fragment of (b)(i) or (b)(ii) which is at least 6 amino acids in length.

under conditions to provide for expression of the polypeptide; and optionally

(II) recovering the expressed polypeptide.

28. (Withdrawn) A process for producing a polypeptide according to claim 22 which comprises chemical synthesis.

29. (Withdrawn) A method of identifying a substance that binds specifically to

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5), NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length

which method comprises:

(A) contacting a candidate substance with (a) and (b) under conditions which allow specific binding; and

(B) determining whether the candidate substance binds to (a) and (b).

30. (Withdrawn) A method according to claim 29 which comprises:

contacting the candidate substance with an agent which comprises:

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5) or NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length; and

(B) determining whether the candidate substance binds to the agent.

31. (Withdrawn) A bi- or oligo- specific antibody, fragment or derivative thereof which is able to bind to both:

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5) or NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length.

32. (Withdrawn) An antibody, fragment or derivative according to claim 31 which is labelled with a detectable label.

33. (Withdrawn) A process for making an antibody as defined in claim 31 comprising culturing a cell that expresses the antibody and optionally purifying antibody from the cell.

34. (Withdrawn) A process according to claim 33 in which the cell is one which is obtainable by administering to a mammal, a polypeptide agent which comprises:

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5) or NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length

extracting B cells from the mammal and selecting a cell from these based on the ability to express an antibody with the specificity such that it is able to bind both

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5) or NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length

35. (Withdrawn) A process according to claim 33 in which the cell is recombinant for a polynucleotide which expresses the antibody.

36. (Withdrawn) A solid support comprising an antibody according to claim 31.

37. (Withdrawn) A solid support according to claim 36 which is a particle, dipstick or microtitre plate.

38 and 39. (Cancelled).

40. (Withdrawn) A diagnostic kit comprising:

(a) a bi or oligo specific first binding substance that is able to bind to both

(I) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(II) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5), NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iv) a fragment of (i) or (ii) which is at least 6 amino acids in length; or

(b) a first binding substance and an agent as defined in claim 3;

wherein optionally the binding substance and/or the agent is labelled.

41. (Withdrawn) A kit according to claim 40 wherein the first binding substance comprises

(a) bi- or oligo-specific binding substance;

(b) a mixture of mono-specific binding substances

(c) natriuretic receptor GC-A (SEQ ID NO: 33)

(d) homologous sequence having at least 70% identity to (c)

(e) a fragment of (c) or (d) which is at least 400 amino acids in length

(f) an extracellular binding domain of the natriuretic receptor GC-A (SEQ ID NO: 34)

and/or is present on a solid support comprising a bi- or oligo- specific antibody, fragment or derivative thereof which is able to bind to both:

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5) or NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length.

42. (Withdrawn) A kit according to claim 40 wherein the agent comprises

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5), NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length.

43. (Withdrawn) Use of:

- a first binding substance as defined in, or

- an agent

- a polynucleotide or its complement that encodes said first binding substance or agent

- a bi or oligo specific antibody fragment or derivative thereof which is able to bind said first binding substance or agent

- a solid support which comprises said antibody; or

- a kit comprising said bi or oligo specific first binding substance and said agent

wherein said first binding substance or agent comprises:

(a) (i) proANP (SEQ ID NO. 1), ANP (SEQ ID NO. 2) or NT-proANP (SEQ ID NO. 3);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length;

and

(b) (i) proBNP (SEQ ID NO. 4), BNP (SEQ ID NO. 5), NT-proBNP (SEQ ID NO. 6);

(ii) a homologous sequence having at least 70% identity to (i); or

(iii) a fragment of (i) or (ii) which is at least 6 amino acids in length

in a method for diagnosis and/or monitoring treatment of heart failure.

44. (Withdrawn) A method of diagnosing and/or monitoring treatment of heart failure in an individual comprising:

(a) obtaining a biological sample from an individual;

(b) determining the activation or inactivation of both the ANP and BNP hormonal systems in the individual by a method which comprises simultaneously detecting the presence or amount of proANP and proBNP or fragments thereof in the sample.

45. (Cancelled).

46. (Currently Amended) The method of claim 2, wherein the first binding substance is able to bind to ~~both~~:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3);

(ii) a species homologue or allelic variant of (a)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (a)(i) or (a)(ii); or

(iv) a fragment of (a)(i), (a)(ii), or (a)(iii) which is at least 6 amino acids in length;

~~and~~

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a species homologue or allelic variant of (a)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (b)(i) or (b)(ii); or

(iv) a fragment of (b)(i), (b)(ii), or (b)(iii) which is at least 6 amino acids in length; and

(c) a fusion polypeptide agent comprising both (a) and (b).

47. (Currently Amended) The method according to claim 1 which comprises contacting the sample with

- ~~an~~ a fusion polypeptide agent comprising both:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3);

(ii) a species homologue or allelic variant of (a)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (a)(i) or (a)(ii); or

(iv) a fragment of (a)(i), (a)(ii), or (a)(iii) which is at least 6 amino acids in length; and

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a species homologue or allelic variant of (b)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (b)(i) or (b)(ii); or

(iv) a fragment of (b)(i), (b)(ii), or (b)(iii) which is at least 6 amino acids in length. and

- a first binding substance which is able to bind to:

(c) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3);

(ii) a species homologue or allelic variant of (c)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (c)(i) or (c)(ii) ; or

(iv) a fragment of (c)(i), (c)(ii), or (c)(iii) which is at least 6 amino acids in length; ~~and/or~~

(d) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a species homologue or allelic variant of (d)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (d)(i) or (d)(ii); or

(iv) a fragment of (d)(i), (d)(ii), or (d)(iii) which is at least 6 amino acids in length; and

(e) said fusion polypeptide agent.

48. (Currently Amended) The method of claim 5, wherein the first binding substance comprises

(a) natriuretic receptor GC-A (SEQ ID NO: 33); or

(b) ~~a species homologue or allelic variant of (a);~~

~~(c) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (a) or (b); or~~

~~(d)~~ a fragment of (a)~~, (b), or (c)~~ which is at least 400 amino acids in length.

49. (Currently Amended) ~~Agent~~ The fusion polypeptide agent of claim 18, which comprises both:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3);

(ii) a species homologue or allelic variant of (a)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (a)(i) or (a)(ii); or

(iv) a fragment of (a)(i), (a)(ii), or (a)(iii) which is at least 6 amino acids in length; and

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a species homologue or allelic variant of (b)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (b)(i) or (b)(ii); or

(iv) a fragment of (b)(i), (b)(ii), or (b)(iii) which is at least 6 amino acids in length.

50. (Previously Presented) A polynucleotide according to claim 24 which comprises:

(a) (i) SEQ ID NO:7, 8, or 9;

(ii) a species homologue or allelic variant of (a)(i);

(iii) a sequence complementary to (a)(i) or (a)(ii);

(iv) a sequence which hybridises under medium or high stringent conditions to (a)(i), (a)(ii), or (a)(iii);

(v) a sequence which is degenerate as a result of the genetic code to (a)(i), (a)(ii), (a)(iii), or (a)(iv);

(vi) a sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to any of the sequences in (a)(i) to (a)(v); or

(vii) a fragment of any of the sequences in (a)(i) to (a)(vi), wherein said fragment encodes a peptide of at least six amino acids in length;

and

(b) (i) SEQ ID NO:10, 11, or 12;

(ii) a species homologue or allelic variant of (b)(i);

(iii) a sequence complementary to (b)(i) or (b)(ii);

(iv) a sequence which hybridises under medium or high stringent conditions to (b)(i), (b)(ii), or (b)(iii);

(v) a sequence which is degenerate as a result of the genetic code to (b)(i), (b)(ii), (b)(iii), or (b)(iv);

(vi) a sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to any of the sequences in (b)(i) to (b)(v); or

(vii) a fragment of any of the sequences in (b)(i) to (b)(vi), wherein said fragment encodes a peptide of at least six amino acids in length.

51. (Currently Amended) The process of claim 27, wherein the fusion polypeptide agent comprises both:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3);

(ii) a species homologue or allelic variant of (a)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (a)(i) or (a)(ii); or

(iv) a fragment of (a)(i), (a)(ii), or (a)(iii) which is at least 6 amino acids in length; and

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a species homologue or allelic variant of (b)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (b)(i) or (b)(ii); or

(iv) a fragment of (b)(i), (b)(ii), or (b)(iii) which is at least 6 amino acids in length.

52. (Currently Amended) The method of claim 46, wherein the first binding substance binds to both:

- the homologous sequence of (a)(iii) or a fragment of (a)(iii) that is at least 6 amino acids in length, ~~and~~ or the peptide of (a)(i), (a)(ii), or a fragment of (a)(i) or (a)(ii) which is at least 6 amino acids in length, and

- the homologous sequence of (b)(iii) or a fragment of (b)(iii) that is at least 6 amino acids in length, ~~and~~ or the peptide of (b)(i), (b)(ii), or a fragment of (b)(i) or (b)(ii) which is at least 6 amino acids in length.

53. (Previously Presented) The method of claim 46, wherein:

- the homologous sequence of (a)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to the first binding substance which also binds to a sequence of (a)(i); and

- the homologous sequence of (b)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to the first binding substance, which also binds to a sequence of (b)(i).

54. (Previously Presented) The method of claim 47, wherein:

- the homologous sequence of (a)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to a binding substance, which also binds to a sequence of (a)(i);

- the homologous sequence of (b)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to a binding substance, which also binds to a sequence of (b)(i);

- the homologous sequence of (c)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to said first binding substance, which also binds to a sequence of (c)(i); and

- the homologous sequence of (d)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to said first binding substance, which also binds to a sequence of (d)(i).

55. (Previously Presented) The method of claim 48, wherein the homologous sequence of (c) or a fragment thereof that is at least 6 amino acids in length is capable of binding to a second binding substance, which also binds to the sequence of (a).

56. (Currently Amended) The fusion polypeptide agent of claim 49, wherein:

- the homologous sequence of (a)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to a binding substance, which also binds to a sequence of (a)(i); and

- the homologous sequence of (b)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to a binding substance, which also binds to a sequence of (b)(i).

57. (Previously Presented) The polynucleotide of claim 50, wherein:

- the sequence of (a)(vi) or a fragment thereof encodes a sequence that is at least six amino acids in length and is capable of binding to a binding substance, which also binds to a sequence encoded by a sequence of (a)(i); and

- the sequence of (b)(vi) or a fragment thereof encodes a sequence that is at least six amino acids in length and is capable of binding to a binding substance, which also binds to a sequence encoded by a sequence of (b)(i).

58. (Previously Presented) The process of claim 51, wherein:

- the homologous sequence of (a)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to a binding substance, which also binds to a sequence of (a)(i); and

- the homologous sequence of (b)(iii) or a fragment thereof that is at least 6 amino acids in length is capable of binding to a binding substance, which also binds to a sequence of (b)(i).

59. (Currently Amended) The method of claim 3, wherein the first binding substance is able to bind to:

(a) (i) proANP (SEQ ID NO:1), ANP (SEQ ID NO:2), or NT-proANP (SEQ ID NO:3);

(ii) a species homologue or allelic variant of (a)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (a)(i) or (a)(ii); or

(iv) a fragment of (a)(i), (a)(ii), or (a)(iii) which is at least 6 amino acids in length; ~~and/or~~

(b) (i) proBNP (SEQ ID NO:4), BNP (SEQ ID NO:5), or NT-proBNP (SEQ ID NO:6);

(ii) a species homologue or allelic variant of (a)(i);

(iii) a homologous sequence having at least 70%, 75%, 80%, 90%, 95%, 97%, or 99% identity to (b)(i) or (b)(ii); or

(iv) a fragment of (b)(i), (b)(ii), or (b)(iii) which is at least 6 amino acids in length; and

(c) said fusion polypeptide agent.

60. (Currently Amended) The method of claim ~~49~~ 47, wherein the first binding substance binds to:

- the homologous sequence of (a)(iii) or a fragment of (a)(iii) that is at least 6 amino acids in length, and the peptide of (a)(i), (a)(ii), or a fragment of (a)(i) or (a)(ii) which is at least 6 amino acids in length, ~~and/or~~ and

- the homologous sequence of (b)(iii) or a fragment of (b)(iii) that is at least 6 amino acids in length, and the peptide of (b)(i), (b)(ii), or a fragment of (b)(i) or (b)(ii) which is at least 6 amino acids in length.

61. (New) The method of claim 1, wherein detecting the presence or proportionally cumulative amount of atrial and brain natriuretic peptide prohormones (proANP and proBNP) or fragments thereof in the sample is done relative to a reference level for determining activation or inactivation of the ANP and BNP hormonal systems.